

1350971

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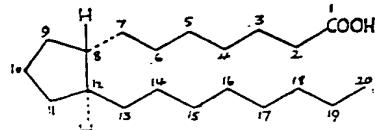
## (54) CYCLOPENTANE DERIVATIVES

(71) We, IMPERIAL CHEMICAL INDUSTRIES LIMITED, Imperial Chemical House, Millbank, London, SW1P 3JF, a British Company, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new cyclopentane derivatives, and in particular it relates to new cyclopentane derivatives which are analogues of the naturally occurring compounds known as prostaglandin F<sub>2α</sub> and prostaglandin E<sub>2</sub>, showing a similar spectrum of pharmacological properties and being useful for similar purposes. The relative potency of the new compounds, however, in respect of the particular pharmacological effects shown is different from that of the above naturally occurring prostaglandins, and in particular they are more potent as luteolytic agents than the corresponding natural prostaglandins. That is to say, the prostaglandin F<sub>2α</sub> analogues of the present invention are more potent than natural prostaglandin F<sub>2α</sub>, and the prostaglandin E<sub>2</sub> analogues of the present invention are more

potent than natural prostaglandin E<sub>2</sub>. The new compounds are, in a similar way, more potent as stimulants of uterine smooth muscle than the corresponding natural prostaglandins F<sub>2α</sub> and E<sub>2</sub>, and the prostaglandin E<sub>2</sub> analogues of the invention are particularly valuable in this respect. The new compounds are therefore advantageous when used as contraceptives, for the termination of pregnancy or for control of the oestrus cycle, as hypotensives or for the relief of bronchospasm. The new compounds of the invention are also useful for addition to semen intended for artificial insemination of domestic animals, the success rate of insemination being thereby increased, especially in pigs.

The cyclopentane derivatives described in this specification will be named as derivatives of prostanoic acid of the formula shown below and numbered as shown:—



[Price 25p]



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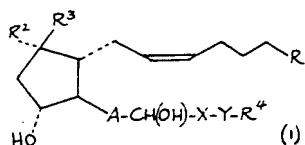
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According to the invention there is provided a prostanoic acid derivative of the formula:—



- 5 wherein R<sup>1</sup> is a hydroxymethyl or carboxy radical, or an alkoxy carbonyl radical of up to 11 carbon atoms; either R<sup>2</sup> is a hydroxy radical or an alkanoyloxy radical of 1 to 4 carbon atoms and R<sup>3</sup> is a hydrogen atom, or R<sup>2</sup> and R<sup>3</sup> together form the oxo radical;
- 10 A is an ethylene or transvinylene radical; X is an alkylene radical of 1 to 3 carbon atoms bearing as substituents 0, 1 or 2 alkyl radicals, each of 1 to 3 carbon atoms; Y is an oxygen or sulphur atom, a sulphinyl (—SO—) radical or an alkylimino (-NAlkyl-) radical of up to 4 carbon atoms; and R<sup>4</sup> is an aryl, benzyl or furfuryl radical which is unsubstituted or which is substituted by hydroxy or halogen atoms, nitro or phenyl radicals, alkyl, alkenyl, halogenoalkyl, alkoxy, alkenyloxy or acylamino radicals of up to 4 carbon atoms or dialkylamino radicals wherein each alkyl is of 1 to 3 carbon atoms; which compound contains 0 or 1 alkyl radicals of up to 4 carbon atoms on carbon atoms 2, 3 or 4; and for those compounds wherein R<sup>1</sup> is a carboxy radical, the pharmaceutically acceptable salts thereof.
- 15 A suitable value for R<sup>1</sup> when it is an alkoxy carbonyl radical of up to 11 carbon atoms is, for example, the methoxycarbonyl ethoxy carbonyl, n-butoxycarbonyl or n-decyloxycarbonyl radical, preferably an alkoxy carbonyl radical of up to 6 or 7 carbon atoms.
- 20 A suitable value for R<sup>2</sup> when it is an alkanoyloxy radical of 1 to 4 carbon atoms is, for example, the acetoxy or propionyloxy radical.
- 25 A suitable value for X when it is an alkylene radical of 1 to 3 carbon atoms bearing as substituents 0, 1 or 2 alkyl radicals, each of 1 to 3 carbon atoms is, for example a methylene, ethylene or trimethylene radical bearing 0, 1 or 2 methyl substituents, for example the methylene, ethylidene, isopropylidene and trimethylene radicals.
- 30 A suitable value for Y when it is an alkylimino radical of up to 4 carbon atoms is, for example, the methylimino (CH<sub>3</sub>-N<) radical.
- 35 A suitable value for A is the *trans*-vinylene radical.
- 40 A suitable value for R<sup>4</sup> when it is an aryl radical optionally substituted, is for example a phenyl, naphthyl, or furfuryl benzyl radical optionally substituted by not more than two halogen atoms, phenyl, hydroxy, methyl, t-butyl, allyl, methoxy, or allyloxy radicals, chloro-
- 45
- 50
- 55

allyl or fluoroalkyl each of 1 to 4 carbon atoms or dimethylamino radicals.

Suitable halogen atom substituents in R<sup>4</sup> are, for example, chlorine, bromine or fluorine atoms. Suitable alkyl, alkoxy, alkenyl or alkenyloxy substituents of up to 4 carbon atoms in R<sup>4</sup> are, for example methyl, t-butyl, allyl, methoxy or allyloxy radicals. Suitable halogenoalkyl substituents of 1 to 4 carbon atoms in R<sup>4</sup> are, for example chloroalkyl or fluoroalkyl radicals, for example trifluoromethyl radicals. Suitable dialkylamino radicals wherein each alkyl is of 1 to 3 carbon atoms, which may be substituents in R<sup>4</sup> are, for example, dialkylamino radicals wherein the two alkyl radicals are the same, for example the dimethylamino radical.

Suitable substituted aryl radicals are for example, chlorophenyl, chloronaphthyl, bromophenyl, fluorophenyl, tolyl, xylyl, methyl-naphthyl, t-butylphenyl, methylchlorophenyl, trifluoromethylphenyl, hydroxyphenyl, methoxyphenyl, methoxynaphthyl, biphenyl, dimethylaminophenyl and tetrahydronaphthyl radicals.

Preferred aryl radicals contain not more than two substituents as defined above. Particular values for R<sup>4</sup> are, therefore, the phenyl, benzyl, furfuryl, 1-naphthyl, 2-naphthyl, 2-, 3- and 4-chlorophenyl, 4-bromophenyl, 2-, 3- and 4-fluorophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dichlorophenyl, 2-, 3- and 4-tolyl, 2,3-, 3,4- and 3,5-xylyl, 4-t-butylphenyl, 3-allylphenyl, 3-trifluoromethylphenyl, 4-hydroxyphenyl, 2-, 3- and 4-methoxyphenyl, 4-biphenyl, 3-dimethylaminophenyl, 2-chloro-4-methylphenyl, 1-chloro-2-naphthyl, 4-chloro-2-naphthyl, 6-methyl-2-naphthyl, 6-methoxy-2-naphthyl and 5,6,7,8-tetrahydro-2-naphthyl radicals.

A suitable value for the alkyl radical of up to 4 carbon atoms which may be present as a substituent on carbon atom 2, 3 or 4 is, for example the methyl radical.

Examples of base-addition salts are the ammonium, alkyl-ammonium containing 1 to 4 alkyl radicals each of 1 to 6 carbon atoms, alkanolammonium containing 1 to 3 2-hydroxyethyl radicals, and alkali metal salts, for example the triethylammonium, ethanolammonium, diethanolammonium, sodium and potassium salts.

It will be observed that the compounds of the formula I contain at least five asymmetric carbon atoms, namely carbon atoms 8, 9, 11, 12 and 15, the configurations at four of which, 8, 9, 11 and 12 are specified in formula I, and that carbon atoms 2, 3 and 4 may also be asymmetrically substituted, so that it is clear that such compounds can exist in at least two optically active forms. It is to be understood that the useful properties of the racemate may be present to differing extents in the optical isomers, and that this invention relates

to the racemic form of the compounds of formula I and any optically active form which shows the above useful properties, it being a matter of common general knowledge how the 5 optically active forms may be obtained, and to determine their respective biological properties.

It is also to be understood that the above definition encompasses both C-15 epimers and 10 that in all chemical formulae shown hereafter in this specification, the same fixed stereo-chemistry at C-8, 9, 11 and 12 as that shown in formula I is implied.

Although both C-15 epimers of a compound 15 of the invention possess desirable pharmacological properties, that epimer which is more polar on thin layer chromatography is the more active, for example in the luteolytic test, and the more polar C-15 epimers are therefore preferred.

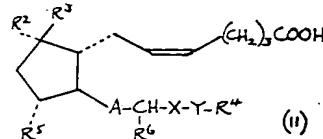
A preferred group of cyclopentane derivatives of the invention, because of their high luteolytic or smooth muscle stimulant properties, comprises those compounds wherein 25  $R^4$  is a chlorophenyl, fluorophenyl, trifluoromethylphenyl or unsubstituted naphthyl radical, especially those compounds wherein  $R^1$  is the carboxy, methoxycarbonyl or hydroxymethyl radical, and particularly those compounds wherein  $R^4$  is the 3- or 4-chlorophenyl, 2- or 4-fluorophenyl, 3-trifluoromethylphenyl or unsubstituted naphthyl radical. A particularly preferred sub-group comprises those compounds wherein  $R^1$  is the carboxy, 30 methoxycarbonyl or hydroxymethyl radical,  $R^2$  is the hydroxy radical and  $R^3$  is a hydrogen atom, or  $R^2$  and  $R^3$  together form the oxo radical, A is the *trans*-vinylene radical, X is the methylene or isopropylidene radical, Y is an oxygen atom and  $R^4$  is the 3- or 4-chlorophenyl, 2- or 4-fluorophenyl, 3-trifluoromethylphenyl or 2-naphthyl radical, optionally bearing a methyl substituent on carbon atom 2.

Particular preferred compounds of the invention are 16 - (4 - fluorophenoxy)- $\alpha,11\alpha,15$  - trihydroxy - 17,18,19,20 - tetrnor - 5 - *cis* - 13 - *trans* - prostadienoic acid, methyl 16 - (4 - fluorophenoxy) -  $\alpha,11\alpha,15$  - trihydroxy - 17,18,19,20 - tetrnor - 5 - *cis* - 13 - *trans* - prostadienoic acid, 16 - (4 - chlorophenoxy) -  $\alpha,11\alpha,15$  - trihydroxy - 17,18,19,20 - tetrnor - 5 - *cis* - 13 - *trans* - prostadienoic acid, 16 - (4 - chlorophenoxy) -  $\alpha,11\alpha,15$  - trihydroxy - 17,18,19,20 - tetrnor - 5 - *cis* - 13 - *trans* - prostadienoic acid, 16 - (3 - chlorophenoxy) -  $\alpha,11\alpha,15$  - trihydroxy - 17,18,19,20 - tetrnor - 5 - *cis* - 13 - *trans* - prostadienoic acid, 16 - methyl 16 - (3 - chlorophenoxy) -  $\alpha,11\alpha,15$  - trihydroxy - 17,18,19,20 - tetrnor - 5 - *cis* - 13 - *trans* - prostadienoic acid.

trihydroxy - 17,18,19,20 - tetrnor - 5 - *cis* - 13 - *trans* - prostadienoate, 16 - (3 - chlorophenoxy) -  $\alpha,11\alpha,15$  - trihydroxy - 2 - methyl - 17,18,19,20 - tetrnor - 5 - *cis* - 13 - *trans* - prostadienol,  $\alpha,11\alpha,15$  - trihydroxy - 16 - (3 - trifluoromethylphenoxy) - 17,18,19,20 - tetrnor - 5 - *cis* - 13 - *trans* - prostadienoic acid,  $\alpha,11\alpha,15$  - trihydroxy - 16 - (2 - naphthoxy) - 17,18,19,20 - tetrnor - 5 - *cis* - 13 - *trans* - prostadienoic acid, 16 - (4 - chlorophenoxy) -  $\alpha,11\alpha,15$  - trihydroxy - 16,16 - dimethyl - 17,18,19,20 - tetrnor - 5 - *cis* - 13 - *trans* - prostadienoic acid and 16 - (4 - chlorophenoxy) -  $\alpha,11\alpha,15$  - dihydroxy - 9 - oxo - 17,18,19,20 - tetrnor - 5 - *cis* - 13 - *trans* - prostadienoic acid.

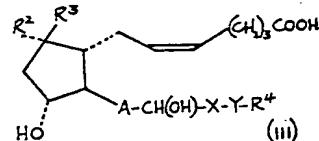
The cyclopentane derivatives of the invention may be manufactured by methods known in themselves for the manufacture of chemically analogous compounds. Thus, the following processes for the manufacture of the cyclopentane derivative of the formula I, are provided as further features of the invention:

(a) for those compounds wherein  $R^1$  is a carboxy radical, the hydrolysis of a compound of the formula:



or of a mixed anhydride thereof, wherein A, X, Y,  $R^2$ ,  $R^3$  and  $R^4$  have the meanings stated above, and  $R^5$  and  $R^6$  are each a tetrahydropyran - 2 - yloxy radical, or an acyloxy radical of 1 to 6 carbon atoms, whereafter when a salt is required the product is reacted with a base; or

(b) for those compounds wherein  $R^1$  is an alkoxy carbonyl radical of up to 11 carbon atoms, the reaction of an acid of the formula:



wherein A, X, Y,  $R^2$ ,  $R^3$  and  $R^4$  have the meanings stated above, with a diazoalkane of the formula  $R^7N_2$ , wherein  $R^7$  is an alkyl radical of 1 to 10 carbon atoms; or

(c) for those compounds wherein  $R^1$  is an alkoxy carbonyl radical of up to 11 carbon atoms, the reaction of a salt, for example the silver salt, of an acid of the formula III, with an alkyl halide of 1 to 10 carbon atoms, for example the alkyl iodide; or

(d) for those compounds wherein  $R^1$  is the

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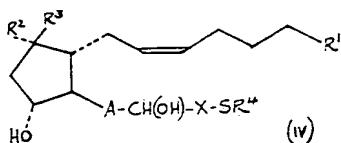
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- hydroxymethyl radical and Y is the oxygen or sulphur atom, or an alkylimino radical, the reduction of an ester of the formula I wherein R<sup>1</sup> is an alkoxy carbonyl radical, for example an alkoxy carbonyl radical of up to 11 carbon atoms, for example with a complex metal hydride, for example lithium aluminium hydride, or
- (e) for those compounds wherein Y is the sulphonyl radical, the oxidation of a thio-compound of the formula:—

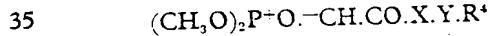


wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, A and X have the meanings defined in claim 1, for example with sodium periodate.

A suitable mixed anhydride is a mixed anhydride with a lower alkanoic acid, for example a lower alkanoic acid of up to 8 carbon atoms, for example acetic acid.

The hydrolysis in process (a) may be carried out under either acidic or basic conditions, for example in aqueous acetic acid, or in an aqueous or alcoholic solution of an alkali metal carbonate, for example potassium carbonate in methanol, and it may be carried out at ambient temperature or at an elevated temperature of up to 60° C.

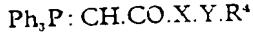
The starting material of the formula II wherein A is a trans-vinylene radical, and Y is an oxygen or sulphur atom, used in the process of the invention may be obtained by reaction of the known aldehyde V (Ac = acetyl or p-phenylbenzoyl) with a phosphonate of the formula



(which is prepared from dimethyl methylphosphonate and an ester of the formula



in the presence of butyllithium), or with a phosphorane of the formula



(which is prepared from triphenylphosphine and a compound of the formula



to give an unsaturated ketone VI. The ketone VI is reduced with zinc borohydride to the corresponding unsaturated alcohol VII, and the protecting acyl group is then removed with potassium carbonate in methanol to give a diol VIII. The diol VIII is protected as a bis-tetrahydropyranyl ether and the lactone ring is then reduced with di-isobutyl aluminium hydride to give a lactol X, or alternatively the diol VIII is reduced with disobutyl aluminium hydride to give a triol which may be acylated and selectively hydrolysed to give the lactol bis-ester (X, R<sup>5</sup>=R<sup>6</sup>=acyloxy). The lactol X is reacted with the phosphonium ylide anion obtained from (4-carboxybutyl)-triphenylphosphonium bromide and a strong base, to give a carboxylic acid of the formula II.

The starting material of the formula II wherein A is an ethylene radical, and Y is an oxygen or sulphur atom, used in the process of the invention, may be obtained by hydrogenating an unsaturated ketone VI in the presence of 5% palladium-on-carbon catalyst, or with nickel boride, to give a saturated ketone XI, and repeating the procedure outlined above using the saturated ketone XI in place of the unsaturated ketone VI.

The starting material of the formula II wherein R<sup>2</sup> is an alkanoyloxy radical may be obtained from the corresponding compound wherein R<sup>2</sup> is a hydroxy radical by acylation with an acid anhydride in pyridine to give a 9-ester-1-mixed anhydride.

The starting material of the formula II, III or IV wherein R<sup>2</sup> and R<sup>3</sup> together form the oxo radical, may be obtained from the corresponding starting material of the formula II, wherein R<sup>2</sup> is hydroxy and R<sup>3</sup> is hydrogen, by oxidation with Jones' reagent (chromic acid in ketone), followed, as required, by hydrolysis of the tetrahydropyranyl protecting groups and esterification of the carboxylic acid group.

It is, of course, to be understood that an optically active compound of the invention may be obtained either by resolving the corresponding racemate, or by carrying out the above-described reaction sequences starting from an optically active intermediate, for example from an optically active aldehyde of the formula IV (Ac = acetyl or p-phenylbenzoyl).

composition of the invention is a sterile, substantially aqueous, injectable solution.

The compositions of the invention may be prepared by conventional means, and may 5 incorporate conventional excipients.

The invention is illustrated, but not limited, by the following Examples:—

Example 1.

A solution of  $9\alpha$ -hydroxy - 16 - phenoxy-  
10  $11\alpha,15$  - bis(tetrahydropyran - 2 - yloxy)-  
17,18,19,20 - tetrnor - 5 - cis - 13 - trans-  
prostadienoic acid (120 mg.) in 1.5 ml. of 2:1  
mixture of acetic acid and water, was stirred  
15 at 50° C. for 4 hours. The solvents were  
evaporated, the residue was dissolved in dilute  
aqueous sodium bicarbonate solution (2 ml.)  
and the solution was extracted with ethyl  
acetate ( $3 \times 2$  ml.) and the extracts were  
20 discarded. The aqueous solution was acidified  
to pH 3—4 with 2N aqueous oxalic acid and  
the acidified solution was extracted with ethyl  
acetate ( $4 \times 5$  ml.). The ethyl acetate extracts  
were washed with a 1:1 mixture of saturated  
25 brine and water, and were then dried.  
After evaporation of the ethyl acetate, the  
residue consisted of a mixture of the C-15  
epimers of  $9\alpha,11\alpha,15$  - trihydroxy - 16-  
30 phenoxy - 17,18,19,20 - tetrnor - 5 - cis-  
13 - trans - prostadienoic acid. Thin-layer  
chromatography on silica gel plates, supplied  
commercially by Merck of Darmstadt, using  
35 a mixture of benzene: dioxan: acetic acid  
(20:10:1) as the developing solvent, separated  
the C-15 epimers, having  $R_F$  values of  
0.3 and 0.4, respectively. (Throughout this  
Example  $R_F$  values refer to silica gel plates  
40 supplied commercially by Merck of Darmstadt,  
and the spots were detected either by  
fluorescence, or by spraying the plates with a  
solution of ceric ammonium nitrate in sulphuric  
acid). The n.m.r. spectrum of each isomer  
45 (in deuterated acetone) showed the following  
characteristic bands ( $\delta$  values):—

- 5.6—6.1, broad multiplet, 5 aromatic protons
- 4.2—4.8, broad multiplets, 4 olefinic protons
- 2.9—3.8, broad multiplets, 3H,  $H-C-O$   
and 4 exchangeable protons

The bis-tetrahydropyranyl ether used as starting material may be prepared as follows:—

n-Butyl lithium (69 ml. of a 1.2M solution in hexane) was added to a solution of dimethyl methylphosphonate (10.3 g.) in dry tetrahydrofuran at -78° C. in an atmosphere of nitrogen. After 10 minutes, a solution of phenoxyacetyl chloride (4.1 g.) in dry tetrahydrofuran (20 ml.) was added dropwise, and the mixture was stirred for 4 hours at -78° C. The reaction mixture was neutralised with acetic acid and the solvents were removed under reduced pressure. The residue was shaken with a mixture of ether (100 ml.) and

water (20 ml.), and the organic phase was separated and washed with brine. The solution was dried, the solvents were evaporated and the residue was distilled in a bulb distillation apparatus at an oven temperature of 160° C. and 0.1 mm. pressure, to give dimethyl 2 - oxo - 3 - phenoxypropylphosphonate.

A solution of dimethyl 2 - oxo - 3 - phenoxypropylphosphonate (1.01 g.) in dry 1,2-dimethoxyethane (20 ml.) at -78° C. was treated with n-butyl-lithium (2.75 ml. of a 1.2M solution in hexane), and the mixture was stirred for 15 minutes. To this mixture was added a solution of  $4\beta$  - formyl - 2,3,3a $\beta$ ,6a $\beta$ -tetrahydro - 2 - oxo - 5 $\alpha$  - (p - phenylbenzoyloxy)cyclopenteno[b]furan (1.95 g.) in 1,2-dimethoxyethane (10 ml.), and after 1 hour the reaction mixture was neutralised with glacial acetic acid and all solvents were removed by evaporation under reduced pressure below 35° C. The residue was chromatographed on "Florisil" (trade mark) 70 silica using solutions of ethyl acetate in methylene chloride as eluant, to yield the unsaturated ketone product as a white solid. [R<sub>F</sub> = 0.6 (1:1 ethyl acetate/benzene)].

To a solution of the unsaturated ketone (500 mg.) in dry 1,2-dimethoxyethane (20 ml.) at 0° C. was added 1.5 ml. of a 0.5 M solution of zinc borohydride in 1,2-dimethoxyethane. The mixture was stirred at room temperature for 30 minutes, then saturated sodium hydrogen tartrate solution was added until effervescent (10 ml.). 1N Hydrochloric acid (2.1 ml.) was added, the organic layer was separated, washed with a 1:1 mixture of saturated brine and water, then dried. The solvents were evaporated to give a mixture of epimeric unsaturated alcohols. [R<sub>F</sub> = 0.3 (1:1 ethyl acetate/benzene)].

The mixture of epimeric unsaturated alcohols (500 mg.) was stirred vigorously for 2 hours with finely powdered anhydrous potassium carbonate (140 mg.) in methanol (10 ml.). 1N Hydrochloric acid (2.1 ml.) was added, followed by ethyl acetate (50 ml.). The organic layer was separated, washed successively with saturated sodium bicarbonate solution and saturated brine, and dried, and the solvents were evaporated. The residue was chromatographed on Florisil (20 g.). Elution with ether removed by-products, and subsequent elution with ethyl acetate gave a mixture of the C-15 epimeric diols [R<sub>F</sub> = 0.2 (ethyl acetate)].

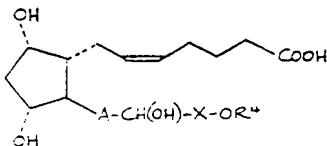
To a solution of the epimeric diols (316 mg.) in methylene chloride (3 ml.) under an atmosphere of nitrogen were added successively redistilled 2,3-dihydrofuran (1.2 ml.) and a solution of anhydrous toluene-p-sulphonic acid in tetrahydrofuran (0.1 ml. of a 1% solution).

After 10 minutes, pyridine (3 drops) were added, followed by ethyl acetate (50 ml.). The solution was washed successively with

- 7 saturated sodium bicarbonate solution and  
65 saturated brine, and was dried. Evaporation  
of the solvents gave a mixture of epimeric  
bis-tetrahydropyranyl ethers as a clear oil.  
[R<sub>F</sub> = 0.6 (ethyl acetate)].  
5 To a solution of the epimeric bis-tetrahydropyranyl ethers (420 mg.) in dry toluene (10  
ml.), under an atmosphere of nitrogen at  
-78° C. was added 1 ml. of a 2.2 mmole/  
10 ml. solution of di-isobutyl aluminium hydride  
in toluene. After 15 minutes the reaction  
was quenched by the dropwise addition of  
methanol (3 ml.) and after a further 15  
minutes at room temperature a mixture of  
15 1:1 saturated brine/water (25 ml.) was  
added, and the mixture was extracted with  
ethyl acetate (3 × 50 ml.). The extract was  
washed with saturated brine, and dried, and  
the solvents were evaporated to give a  
mixture of epimers of 2,3,3aβ,6aβ - tetra-  
20 hydro - 2 - hydroxy - 4β - [4 - phenoxy-  
3 - (tetrahydropyran - 2 - yloxy) - 1 - trans-  
butenyl] - 5α - (tetrahydropyran - 2 - yloxy)-  
85 cyclopenteno[b]furan. [R<sub>F</sub> = 0.4 (1:1 ethyl  
acetate/benzene)].  
25 Finely powdered (4-carboxybutyl)triphenyl-  
90 phosphonium bromide (1.11 g.) was heated to  
100° C. under vacuum for 1 hour. The  
evacuated reaction vessel was filled with an  
atmosphere of dry nitrogen, the solid was  
dissolved in dimethylsulphoxide (5 ml.) and  
95 the solution was cooled to room temperature.  
To this solution was added dropwise  
2.35 ml. of a 2M solution of methanesul-  
phonylmethyl sodium in dimethyl sulphoxide  
30 followed by a solution of the mixture of  
epimers of the cyclopenteno[b]furan bis-  
tetrahydropyranyl ether (400 mg.) in a  
mixture of dimethyl sulphoxide (10 ml.) and  
benzene (2 ml.). The solution was stirred for  
3 hours, and the solvent was removed by  
100 evaporation under reduced pressure at a  
temperature below 40° C. The residue was  
shaken with water (10 ml.) and ethyl acetate  
105 (10 ml.) and the aqueous phase was separated,  
extracted with ethyl acetate (2 × 10 ml.) and  
the extracts discarded. The aqueous solution  
was acidified to pH 3-4 with 2N aqueous  
oxalic acid, and extracted with a mixture of  
110 equal parts of ether and petroleum ether  
(b.p. 40-60° C.) (5 × 10 ml.). The organic  
phase was separated, washed with saturated  
brine and was dried. Evaporation of the sol-  
vents gave 9α - hydroxy - 16 - phenoxy-  
11a,15 - bis(tetrahydropyran - 2 - yloxy)-  
17,18,19,20 - tetrnor - 5 - cis - 13 - trans-  
115 prostadienoic acid as a clear oil. [R<sub>F</sub> = 0.5  
(ethyl acetate)].  
120  
125

## Example 2.

The process described in Example 1 was  
repeated, using the appropriate phosphonate  
reagent, to give the compounds shown below.  
The products were identified by n.m.r.  
spectroscopy and are characterised below  
either by R<sub>F</sub> value on thin layer chromatog-  
raphy, or by accurate mass measurement by  
mass spectrometry of either the molecular ion  
or the (M<sup>+</sup> - methyl) ion, whichever is  
more appropriate, of the tetra(trimethylsilyl)  
derivative, which is prepared by adding to the  
compound to be mass measured bis-trimethyl-  
silyl-trifluoroacetamide containing 1% tri-  
methylchlorosilane (Regisil—trade mark) and  
leaving the mixture for 1 hour. In some cases,  
phosphonate reagent, or the unsaturated ketone  
intermediate in which Ac is p-phenylbenzoyl  
have been characterised and appropriate data  
for these compounds are also given.



| No. | R <sub>4</sub>          | A                                  | X                                   |
|-----|-------------------------|------------------------------------|-------------------------------------|
| 1   | phenyl                  | —CH:CH—                            | —CH <sub>2</sub> —                  |
| 2   | phenyl                  | —CH:CH—                            | —CH(CH <sub>3</sub> )—              |
| 3   | phenyl                  | —CH:CH—                            | —C(CH <sub>3</sub> ) <sub>2</sub> — |
| 4   | phenyl                  | —CH:CH—                            | —(CH <sub>2</sub> ) <sub>2</sub> —  |
| 5   | benzyl                  | —CH:CH—                            | —CH <sub>2</sub> —                  |
| 6   | 2-naphthyl              | —CH:CH—                            | —CH <sub>2</sub> —                  |
| 7   | 4-chlorophenyl          | —CH:CH—                            | —CH <sub>2</sub> —                  |
| 8   | 4-chlorophenyl          | —CH <sub>2</sub> CH <sub>2</sub> — | —CH <sub>2</sub> —                  |
| 9   | 3-chlorophenyl          | —CH:CH—                            | —CH <sub>2</sub> —                  |
| 10  | 2-chlorophenyl          | —CH:CH—                            | —CH <sub>2</sub> —                  |
| 11  | 2,4-dichlorophenyl      | —CH:CH—                            | —CH <sub>2</sub> —                  |
| 12  | 4-bromophenyl           | —CH:CH—                            | —CH <sub>2</sub> —                  |
| 13  | 4-fluorophenyl          | —CH:CH—                            | —CH <sub>2</sub> —                  |
| 14  | 4-tolyl                 | —CH:CH—                            | —CH <sub>2</sub> —                  |
| 15  | 3-tolyl                 | —CH:CH—                            | —CH <sub>2</sub> —                  |
| 16  | 4-t-butylphenyl         | —CH:CH—                            | —CH <sub>2</sub> —                  |
| 17  | 3-trifluoromethylphenyl | —CH:CH—                            | —CH <sub>2</sub> —                  |
| 18  | 4-methoxyphenyl         | —CH:CH—                            | —CH <sub>2</sub> —                  |
| 19  | 2-methoxyphenyl         | —CH:CH—                            | —CH <sub>2</sub> —                  |
| 20  | 4-biphenylyl            | —CH:CH—                            | —CH <sub>2</sub> —                  |

| No. | Isomer*        | Mass spectrum  |                 | Phosphonate<br>b.p. (°C./mm.) | Enone<br>m.p. (°C.)<br>(Formula VI) |
|-----|----------------|--|-----------------|-------------------------------|-------------------------------------|
|     |                | Found  | Calculated      |                               |                                     |
| 1   | mp<br>lp       | M <sup>+</sup> =678.3610<br>M <sup>+</sup> =678                  | 678.3625        | 178—185/0.05                  | 155—158                             |
| 2   | mp<br>lp       | M <sup>+</sup> —CH <sub>3</sub> =677.3540<br>M <sup>+</sup> =692 | 677.3545<br>692 | 175/0.2                       | —                                   |
| 3   | mixed          | M <sup>+</sup> —CH <sub>3</sub> =691.3660                        | 691.3702        | 130/0.1                       | —                                   |
| 4   | mp<br>lp       | M <sup>+</sup> =706.3921<br>M <sup>+</sup> =706                  | 706.3928        | 166—168/0.1                   | 120—122                             |
| 5   | mixed          | M <sup>+</sup> =692.3753   | 692.3781        | 170/0.1                       | 99—101                              |
| 6   | mp             | M <sup>+</sup> =728.3744   | 728.3781        | m.p.=85—86°C.                 | 185—187                             |
| 7   | mp<br>lp       | M <sup>+</sup> —CH <sub>3</sub> =697.2948<br>M <sup>+</sup> =712 | 697.3001<br>712 | 170—173/0.1                   | 132—135                             |
| 8   | mp(a)<br>lp(a) | M <sup>+</sup> =714.3399<br>M <sup>+</sup> =714                  | 714.3391        | 170—173/0.1                   | 132—135                             |
| 9   | mp<br>lp       | M <sup>+</sup> —CH <sub>3</sub> =697.2297<br>M <sup>+</sup> =712 | 697.3000<br>712 | 180/0.2                       | —                                   |
| 10  | mp<br>lp       | M <sup>+</sup> =712.3216<br>M <sup>+</sup> =712                  | 712.3235        | 174—178/0.1                   | 129—132                             |
| 11  | mp             | M <sup>+</sup> —CH <sub>3</sub> =731.2599                        | 731.2609        | —                             | 136—138                             |
| 12  | mixed          | M <sup>+</sup> —CH <sub>3</sub> =741.2485                        | 741.2497        | —                             | —                                   |
| 13  | mp<br>lp       | M <sup>+</sup> =696.3468<br>M <sup>+</sup> =696                  | 696.3529        | —                             | 162                                 |
| 14  | mixed          | M <sup>+</sup> =692.3738   | 692.3781        | 164/0.05                      | 149                                 |
| 15  | mp<br>lp       | M <sup>+</sup> =692.3752<br>M <sup>+</sup> =692                  | 692.3781        | 180/0.5                       | 140—141                             |
| 16  | mixed          | M <sup>+</sup> =734.4213   | 734.4251        | —                             | —                                   |
| 17  | mp<br>lp       | M <sup>+</sup> =746.3467(b)<br>(c)                               | 746.3499        | —                             | 115—117                             |
| 18  | mp<br>lp       | M <sup>+</sup> =708.3717<br>M <sup>+</sup> =708                  | 708.3731        | —                             | —                                   |
| 19  | mp<br>lp       | M <sup>+</sup> =708.3710<br>M <sup>+</sup> =708                  | 708.3731        | —                             | —                                   |
| 20  | mp<br>lp       | M <sup>+</sup> =754.3944<br>M <sup>+</sup> =754                  | 754.3938        | m.p.=63—64°C.                 | —                                   |

\* mp=more polar, lp=less polar isomer on silica gel thin layer chromatography.

(a) products synthesised from respectively the more polar and less polar enol intermediates.

(b) R<sub>F</sub>=0.45 after 2 runs on silica gel t.l.c. with 5% acetic acid in ethyl acetate.

(c) R<sub>F</sub>=0.50 after 2 runs on silica gel t.l.c. as for (b).

In the manufacture of compounds 8, wherein A is an ethylene radical, the unsaturated ketone intermediate is reduced to the saturated ketone as follows:—

- 5      The more polar epimer (epimers at C-3 of the butenyl side-chain) of  $4\beta$  - (4 - *p* - chlorophenoxy - 3 - hydroxybut - 1 - *trans* - enyl) - 2,3,3a $\beta$ ,6a $\beta$  - tetrahydro - 2 - oxo - 5 $\alpha$ - ( *p* - phenylbenzoyloxy)cyclopenteno - [b]furan (360 mg.) was dissolved in ethanol (25 ml.) and the solution was added to nickel boride, previously prepared from nickel acetate (620 mg.) and sodium borohydride (2.5 ml. of a 1 M solution). The mixture was shaken with hydrogen for 3 hours and was then filtered, and the filtrate was evaporated to dryness to give  $4\beta$  - (4 - *p* - chlorophenoxy - 3 - hydroxybutyl) - 2,3,3a $\beta$ ,6a $\beta$  - tetrahydro - 2 - oxo - 5 $\alpha$  - ( *p* - phenylbenzoyloxy)cyclopenteno[b] furan,  $R_F$  = 0.4 (50% ethyl acetate in toluene). The saturated ketone was then used, in place of the unsaturated ketone, in the remainder of the process described in Example 1.

25      Example 3.

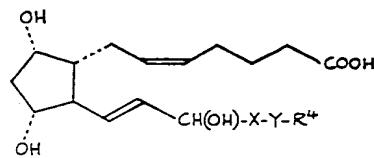
- To a solution of the more polar C-15 epimer of 16 - (4 - chlorophenoxy) - 9 $\alpha$ ,11 $\alpha$ ,15-trihydroxy - 17,18,19,20 - tetrnor - 5 - *cis* - 13 - *trans* - prostadienoic acid (15 mg.) in methanol (1 ml.) at 0° C. was added an excess of a solution of diazomethane in ether. After 10 minutes the solvents were evaporated to give a single C-15 epimer of methyl 16 - (4 - chlorophenoxy) - 9 $\alpha$ ,11 $\alpha$ ,15 - trihydroxy - 17,18,19,20 - tetrnor - 5 - *cis* - 13 - *trans* - prostadienoate as a clear oil,  $R_F$  = 0.3 (ethyl

acetate). The n.m.r. spectrum showed the following characteristic bands ( $\delta$  values):—

- 6.8—7.2, 4 aromatic protons  
5.3—5.7, 4 olefinic protons  
3.6,      COOCH<sub>3</sub>

Example 4.

The process described in Example 1 was repeated, using the appropriate phosphonate reagent, or an equivalent phosphorane R<sup>4</sup>—X—Y—CH<sub>2</sub>.CO.CH:PPH<sub>3</sub>, to give the compounds shown below. The products were identified by n.m.r. spectroscopy and are characterised below either by  $R_F$  value on thin layer chromatography, or by accurate mass measurement by mass spectrometry of the molecular ion of the appropriate fully protected (trimethylsilyl) derivative, which is prepared by adding, to the compound to be mass measured, bis - trimethylsilyltrifluoroacetamide containing 1% trimethylchlorosilane (Regisil trade mark) and leaving the mixture for 1 hour. In some cases, the phosphonate reagent, or the unsaturated ketone intermediate have been characterised and appropriate data for these compounds are also given.



| No. | R <sup>4</sup>                | X                                   | Y                     | Other substituents in prostanoid acid |
|-----|-------------------------------|-------------------------------------|-----------------------|---------------------------------------|
| 21  | phenyl                        | —CH <sub>2</sub> —                  | —N(CH <sub>3</sub> )— | —                                     |
| 22  | 4-chlorophenyl                | —C(CH <sub>3</sub> ) <sub>2</sub> — | —O—                   | —                                     |
| 23  | 4-chlorophenyl                | —CH <sub>2</sub> —                  | —S—                   | —                                     |
| 24  | 3-fluorophenyl                | —CH <sub>2</sub> —                  | —O—                   | —                                     |
| 25  | 2-fluorophenyl                | —CH <sub>2</sub> —                  | —O—                   | —                                     |
| 26  | 3,4-dichlorophenyl            | —CH <sub>2</sub> —                  | —O—                   | —                                     |
| 27  | 2,5-dichlorophenyl            | —CH <sub>2</sub> —                  | —O—                   | —                                     |
| 28  | 2-tolyl                       | —CH <sub>2</sub> —                  | —O—                   | —                                     |
| 29  | 2,3-xylyl                     | —CH <sub>2</sub> —                  | —O—                   | —                                     |
| 30  | 3,5-xylyl                     | —CH <sub>2</sub> —                  | —O—                   | —                                     |
| 31  | 2-chloro-4-methylphenyl       | —CH <sub>2</sub> —                  | —O—                   | —                                     |
| 32  | 3-dimethylaminophenyl         | —CH <sub>2</sub> —                  | —O—                   | —                                     |
| 33  | 1-naphthyl                    | —CH <sub>2</sub> —                  | —O—                   | —                                     |
| 34  | 4-chloro-1-naphthyl           | —CH <sub>2</sub> —                  | —O—                   | —                                     |
| 35  | 2-naphthyl                    | —CH <sub>2</sub> —                  | —O—                   | 2-methyl                              |
| 36  | 6-methyl-2-naphthyl           | —CH <sub>2</sub> —                  | —O—                   | —                                     |
| 37  | 6-methoxy-2-naphthyl          | —CH <sub>2</sub> —                  | —O—                   | —                                     |
| 38  | 3-chlorophenyl                | —CH <sub>2</sub> —                  | —O—                   | 2-methyl                              |
| 39  | 2,3-dichlorophenyl            | —CH <sub>2</sub> —                  | —O—                   | —                                     |
| 40  | 2,6-dichlorophenyl            | —CH <sub>2</sub> —                  | —O—                   | —                                     |
| 41  | 3,5-dichlorophenyl            | —CH <sub>2</sub> —                  | —O—                   | —                                     |
| 42  | 4-chloro-3-methylphenyl       | —CH <sub>2</sub> —                  | —O—                   | —                                     |
| 43  | 3-methoxyphenyl               | —CH <sub>2</sub> —                  | —O—                   | —                                     |
| 44  | 1-chloro-2-naphthyl           | —CH <sub>2</sub> —                  | —O—                   | —                                     |
| 45  | 5,6,7,8-tetrahydro-2-naphthyl | —CH <sub>2</sub> —                  | —O—                   | —                                     |

| No. | Isomer (a) | Mass spectrum   |            | Phosphonate<br>b.p. (°C./mm.) | Enone<br>m.p. (°C.)<br>(Formula VI)* | No. |
|-----|------------|---|------------|-------------------------------|--------------------------------------|-----|
|     |            | Found   | Calculated |                               |                                      |     |
| 21  | mp<br>1p   | M <sup>+</sup> =691.3994<br>691                       | 691.3940   | (b)                           | 145—150                              | 40  |
| 22  | mp<br>1p   | M—CH <sub>3</sub> <sup>+</sup> =725.3302              | 725.3313   | 150/0.05                      | (c)                                  | 41  |
| 23  | mp<br>1p   | M <sup>+</sup> =728.2977                              | 728.3006   | (b)                           | 135—138                              | 42  |
| 24  | mp<br>1p   | M <sup>+</sup> =696.3496<br>696                       | 696.3531   | (d)                           | 138—139                              | 43  |
| 25  | mp<br>1p   | M <sup>+</sup> =696.3510<br>696                       | 696.3531   | (e)                           | 144                                  | 44  |
| 26  | mp<br>1p   | M <sup>+</sup> =746.2791<br>746                       | 746.2844   | (f)                           | 150—152                              | 45  |
| 27  | mp<br>1p   | M <sup>+</sup> =746.2799<br>746                       | 746.2844   | (g)                           | 187—190                              |     |
| 28  | mp<br>1p   | M <sup>+</sup> =692.3813<br>692                       | 692.3781   | 154—160/0.05                  | 165—167                              |     |
| 29  | mp<br>1p   | M <sup>+</sup> =706.3971<br>706                       | 706.3935   | 180/0.15                      | 166—168                              |     |
| 30  | mp<br>1p   | M <sup>+</sup> =706.3922<br>706                       | 706.3935   | —                             | 140—142                              |     |
| 31  | mp<br>1p   | M <sup>+</sup> =726<br>726                            | 726        | —                             | 113—115                              |     |
| 32  | mp<br>1p   | M <sup>+</sup> =721.4020<br>721                       | 721.4047   | (b)                           | 138—145                              |     |
| 33  | mp<br>1p   | M <sup>+</sup> =728.3830<br>728                       | 728.3781   | (h)                           | 185—187                              |     |
| 34  | mp<br>1p   | M <sup>+</sup> =762.3356<br>762                       | 762.3388   | (i)                           | (j)                                  | 5   |
| 35  | mp<br>1p   | M <sup>+</sup> =742.3946<br>742                       | 742.3937   | m.p. 85—86                    | 185—187                              |     |
| 36  | mp<br>1p   | M <sup>+</sup> =742.3902<br>742                       | 742.3937   | m.p. 71—72                    | 153                                  | 10  |
| 37  | mp<br>1p   | M <sup>+</sup> =758.3910<br>758                       | 758.3887   | m.p. 58—59                    | 195                                  | 15  |
| 38  | mp<br>1p   | M <sup>+</sup> =726.3346<br>726                       | 726.3391   | 180/0.2                       | (k)                                  |     |
| 39  | mp<br>1p   | M—CH <sub>3</sub> =731.2644<br>M—CH <sub>3</sub> =731 | 731.2609   | 175/0.03                      | 153—155                              | 20  |

(a) mp  
 (b) the  
 (c) R<sub>F</sub>  
 (d) R<sub>F</sub>  
 (e) R<sub>F</sub>  
 (f) R<sub>F</sub>  
 (g) R<sub>F</sub>  
 (h) R<sub>F</sub>  
 (i) R<sub>F</sub>  
 (j) R<sub>F</sub>  
 (k) R<sub>F</sub>  
 (l) R<sub>F</sub>  
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| No. | Isomer (a)     | Mass spectrum                   |            | Phosphonate<br>b.p. (°C./mm.) | Enone<br>m.p. (°C.)<br>(Formula VI)* |
|-----|----------------|---------------------------------|------------|-------------------------------|--------------------------------------|
|     |                | Found                           | Calculated |                               |                                      |
| 40  | mp<br>lp       | M <sup>+</sup> =746.2844<br>746 | 746.2844   | m.p. 89—90                    | 140—142                              |
| 41  | mp<br>lp       | M <sup>+</sup> 746.2829<br>746  | 746.2844   | m.p. 80—82                    | 138—139                              |
| 42  | mp<br>lp       | M <sup>+</sup> =726.3397<br>726 | 726.3391   | —                             | 143                                  |
| 43  | mp<br>lp       | M <sup>+</sup> =708.3745<br>708 | 708.3730   | (l)                           | 129—130                              |
| 44  | mixed          | M <sup>+</sup> =762.3402        | 762.3391   | m.p. 61—62                    | 195                                  |
| 45  | mp(m)<br>lp(n) |                                 |            |                               |                                      |

(a) mp = more polar, lp = less polar.

(b) these compounds synthesised from phosphoranes (not phosphonates), made as described below.

(c) R<sub>F</sub>=0.5 (50% ethyl acetate in toluene).(d) R<sub>F</sub>=0.2 (40% ethyl acetate in methylene dichloride).(e) R<sub>F</sub>=0.4 (5% acetic acid in ethyl acetate).(f) R<sub>F</sub>=0.3 (50% ethyl acetate in chloroform).(g) R<sub>F</sub>=0.23 (50% ethyl acetate in chloroform).(h) R<sub>F</sub>=0.3 (50% ethyl acetate in methylene dichloride).(i) R<sub>F</sub>=0.4 (10% methanol in ethyl acetate).(j) R<sub>F</sub>=0.8 (50% ethyl acetate in toluene).(k) R<sub>F</sub>=0.6 (50% ethyl acetate in toluene).(l) R<sub>F</sub>=0.4 (50% ethyl acetate in methylene dichloride).(m) R<sub>F</sub>=0.25 (3% acetic acid in ethyl acetate).(n) R<sub>F</sub>=0.30 (3% acetic acid in ethyl acetate).

(m) and (n); δ 6.8 (1H, aromatic), 6.6 (2H, aromatic), 5.4 (2H, olefinic) and 5.7 (2H, olefinic).

\* Ac is p-phenylbenzoyl.

The preparation of a phosphorane, which may be used in place of a phosphonate in the preparation of a cyclopentane derivative of the invention, is exemplified by the preparation of [3 - (3 - dimethylaminophenoxy)-acetylidene] - triphenylphosphorane as follows: —

n-Butyl-lithium (3.85 ml. of a 1.3 M solution in hexane) was added to a solution of 3-dimethylaminophenol (685 mg.) in dimethoxyethane (20 ml.) at -70° C. under an atmosphere of nitrogen. The solution was allowed to warm to room temperature, a solution of 3 - iodoacetylidene - triphenylphosphorane (2.22 g.) in benzene (100 ml.) was added, and the mixture was heated under reflux for 2 hours. The mixture was then diluted with toluene (100 ml.), washed with water (2 × 50 ml.) and dried, the solvents were evaporated and the residue was triturated with ether to give [3 - (3 - dimethylamino-

phenoxy) acetylidene] triphenylphosphorane, m.p. 110—115° C.

In a similar manner were prepared the analogous N-methylanilino (gum) and 4-chlorophenylthio (m.p. 158—165° C.) phosphoranes.

#### Example 5.

The process described in Example 3 was repeated, using the appropriate more polar C-15 epimer, in place of the more polar C-15 epimer of 16 - (4 - chlorophenoxy)-9<sub>α</sub>,11<sub>α</sub>,15 - trihydroxy - 17,18,19,20 - tetranor - 5 - cis - 13 - trans - prostadienoic acid, to give the following methyl esters as single C-15 epimers: —

- a) methyl 16 - (4 - fluorophenoxy)-9<sub>α</sub>,11<sub>α</sub>,15 - trihydroxy - 17,18,19,20 - tetranor - 5 - cis - 13 - trans - prostadienoate, R<sub>F</sub> = 0.3 (5% methanol in toluene) δ = 6.8—7.2 (aromatic), 5.3—5.7 (4 olefinic protons), 3.6 (methyl ester).

- b) methyl  $9\alpha,11\alpha,15$  - trihydroxy - 16 - (2 - naphthoxy) - 17,18,19,20 - tetrnor - 5 - cis - 13 - trans - prostadienoate,  $M^+$  = 670.3542 (calculated 670.3541).  
 5 c) methyl  $9\alpha,11\alpha,15$  - trihydroxy - 2 - methyl - 16 - (2 - naphthoxy) - 17,18,19,20 - tetrnor - 5 - cis - 13 - trans - prostadienoate,  $M^+$  = 684.3678 (calculated 684.3697).  
 10 d) methyl  $9\alpha,11\alpha,15$  - trihydroxy - 16 - (6 - methyl - 2 - naphthoxy) - 17,18,19,20 - tetrnor - 5 - cis - 13 - trans - prostadienoate,  $M^+$  = 684.3739 (calculated 684.3698).  
 15 e) methyl  $9\alpha,11\alpha,15$  - trihydroxy - 16 - (6 - methoxy - 2 - naphthoxy) - 17,18,19,20 - tetrnor - 5 - cis - 13 - trans - prostadienoate,  $M^+$  = 700.3681 (calculated 700.3647).  
 20 f) methyl 16 - (3 - chlorophenoxy) -  $9\alpha,11\alpha,15$  - trihydroxy - 17,18,19,20 - tetrnor - 5 - cis - 13 - trans - prostadienoate,  $R_F$  = 0.3 (ethyl acetate),  $M^+$  = 654.2973 (calculated 654.2995).  
 25 g) methyl  $9\alpha,11\alpha,15$  - trihydroxy - 2 - methyl - 16 - (3 - chlorophenoxy) - 17,18,19,20 - tetrnor - 5 - cis - 13 - trans - prostadienoate,  $R_F$  = 0.4 (ethyl acetate),  $M^+$  = 668.3133 (calculated 668.3151).

#### Example 6.

16 - (4 - Chlorophenoxy) -  $9\alpha,11\alpha,15$  - trihydroxy - 17,18,19,20 - tetrnor - 5 - cis - 13 - trans - prostanoic acid (20 mg. of the more polar C-15 epimer) was treated with an excess of dilute aqueous ammonia to form the ammonium salt. The excess of ammonia was evaporated under reduced pressure, and the residue was treated with the stoichiometric amount of silver nitrate to form the silver salt. The silver salt was filtered off, dried, dissolved in n-butyl iodide (0.5 ml.) and stirred at room temperature for 1 hour. The solution was extracted with ethyl acetate, the ethyl acetate extract was evaporated to dryness, and the residue was chromatographed on Florisil (1 g.) using 50% ethyl acetate in toluene as eluant, to give n-butyl 16 - (4 - chlorophenoxy) -  $9\alpha,11\alpha,15$  - trihydroxy - 17,18,19,20 - tetrnor - 5 - cis - 13 - trans - prostadienoate,  $M^+$  for the tris-(trimethylsilyl) derivative = 696.3427 (calculated 696.3464),  $R_F$  = 0.4 (ethyl acetate).  
 45 In a similar manner, but using ethyl iodide in place of n-butyl iodide, there was obtained ethyl 16 - (4 - chlorophenoxy) -  $9\alpha,11\alpha,15$  - trihydroxy - 17,18,19,20 - tetrnor - 5 - cis - 13 - trans - prostadienoate,  $M^+$  = 668.3086 (calculated 668.3151).

#### Example 7.

A solution of the mixed anhydride of acetic acid and the more polar C-15 epimer of  $9\alpha$  - acetoxy - 16 - (4 - chlorophenoxy) -

$11\alpha,16$  - bis(tetrahydropyran - 2 - yloxy) - 17,18,19,20 - tetrnor - 5 - cis - 13 - trans - prostadienoic acid (73 mg.) in 2 ml. of a 2:1 mixture of acetic acid and water, was stirred at 47° C. under nitrogen for 4 hours. The solvents were evaporated, the residue was dissolved in dilute aqueous sodium bicarbonate solution (2 ml.) and the solution was extracted with ethyl acetate ( $3 \times 2$  ml.). The extracts were discarded, the aqueous solution was acidified to pH 3-4 with 2N aqueous oxalic acid and the acidified solution was extracted with ethyl acetate ( $4 \times 5$  ml.). The ethyl acetate extracts were washed with a 1:1 mixture of saturated brine and water, and were then dried. After evaporation of the ethyl acetate, the residue was purified by thin-layer chromatography on silica gel using 3% acetic acid in ethyl acetate, to give the more polar C-15 epimer of  $9\alpha$  - acetoxy - 16 - (4 - chlorophenoxy) -  $11\alpha,15$  - dihydroxy - 17,18,19,20 - tetrnor - 5 - cis - 13 - trans - prostadienoic acid,  $M^+$  = 682.2942 (calculated 682.2944).

The bis-tetrahydropyranyl ether used as starting material may be prepared as follows:—

A solution of the more polar C-15 epimer of  $9\alpha$ -hydroxy-16-(4-chlorophenoxy)- $11\alpha,15$ -bis(tetrahydropyran - 2 - yloxy) - 17,18,19,20 - tetrnor - 5 - cis - 13 - trans - prostadienoic acid (70 mg.) in 0.15 ml. of a 2:1 mixture of pyridine and acetic anhydride was kept at room temperature for 16 hours. The volatile material was evaporated and cyclohexane (10 ml.) was added to, and boiled off from, the residue three times, leaving the mixed anhydride of acetic acid and  $9\alpha$  - acetoxy - 16 - (4 - chlorophenoxy) -  $11\alpha,15$  - bistetrahydropyran - 2 - yloxy) - 17,18,19,20 - tetrnor - 5 - cis - 13 - trans - prostadienoic acid as a yellow oil,  $\nu_{max}$  ( $\text{CHCl}_3$ ) 1720, 1810  $\text{cm}^{-1}$ .

#### Example 8.

To a solution of  $9\alpha$  - acetoxy - 16 - (4 - chlorophenoxy) -  $11\alpha,15$  - dihydroxy - 17,18,19,20 - tetrnor - 5 - cis - 13 - trans - prostadienoic acid (12 mg.) in methanol (1 ml.) at 0° C. was added an excess of a solution of diazomethane in ether. After 10 minutes, the solvents were evaporated, the residue was dissolved in ether, and the solution was treated with lithium aluminium hydride (50 mg.). The mixture was stirred at room temperature for 1 hour, the excess of hydride was destroyed by the addition of water (1 ml.) and the mixture was extracted with ethyl acetate to give 16 - (4 - chlorophenoxy) -  $9\alpha,11\alpha,15$  - trihydroxy - 17,18,19,20 - tetrnor - 5 - cis - 13 - trans - prostadienol,  $M^+$  = 698.3439 (calculated 698.3441),  $R_F$  = 0.2 (ethyl acetate).

In a similar manner, there were obtained:—  
 16 - (3 - chlorophenoxy) -  $9\alpha,11\alpha,15$  - trihydroxy - 2 - methyl - 17,18,19,20 - tetra-

nor - 5 - *cis* - 13 - *trans* - prostadienol,  
 $R_p = 0.15$  (ethyl acetate,  $M^+ = 712.3575$   
 (calculated 712.3597).

5      9 $\alpha$ ,11 $\alpha$ ,15 - trihydroxy - 16 - (6 - methyl-  
 2 - naphthyloxy) - 17,18,19,20 - tetrnor - 5-  
 cis - 13 - *trans* - prostadienol,  $R_p = 0.2$   
 (ethyl acetate).

10     Example 9.  
 The process described in Example 1 was  
 repeated using the appropriate phosphonate  
 reagent, to give:—

- 15     a) 9 $\alpha$ ,11 $\alpha$ ,15 - trihydroxy - 16 - (4-  
 hydroxyphenoxy) - 17,18,19,20 - tetrnor -  
 5 - *cis* - 13 - *trans* - prostadienoic acid,  
 $R_p = 0.2$  and 0.3 (3% acetic acid in  
 ethyl acetate).  $\delta = 6.82$  (4H, aromatic),  
 5.3—5.7 (4H, olefinic), 3.98—5.1  
 (10H, >CH<sub>2</sub>O— and exchangeable pro-  
 tons); phosphonate,  $R_p = 0.2$  (10%  
 methanol in ethyl acetate); enone\*,  
 m.p. 135—140° C.
- 20     b) 16 - furfuryloxy - 9 $\alpha$ ,11 $\alpha$ ,15 - trihydroxy-  
 17,18,19,20 - tetrnor - 5 - *cis* - 13-  
*trans* - prostadienoic acid,  $R_p = 0.5$  (3%  
 acetic acid in ethyl acetate),  $\delta = 7.5$

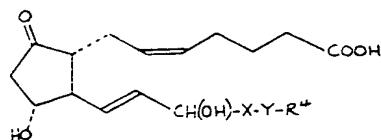
(1H and 6.3 (2H) (furyl protons)  
 5.1—5.6 (4 H, olefinic); phosphonate,  
 b.p. 200° C./0.2 mm; enone\*, m.p. 92—  
 93° C.

c) 16 - (3 - allylphenoxy) - 9 $\alpha$ ,11 $\alpha$ ,15-  
 trihydroxy - 17,18,19,20 - tetrnor - 5-  
*cis* - 13 - *trans* - prostadienoic acid,  
 $M^+ = 718.3892$  (calculated 718.3938);  
 phosphonate,  $R_p = 0.32$  (ethyl acetate);  
 enone\*, m.p. 110—112° C.

\* Formula VI. Ac is *p*-phenylbenzoyl.

#### Example 10

The process described in Example 1 was  
 repeated, using a 9-oxo prostanoic acid derivative  
 in place of a 9 $\alpha$ -hydroxy prostanoic acid  
 derivative, to give the compounds shown  
 below. For measurement of mass spectra,  
 the acids were converted to methyl esters with  
 diazomethane, the 9-oxo group was protected  
 by conversion to the methoxime with  
 methoxylamine, and, where indicated, the  
 hydroxy groups at C-11 and C-15 were pro-  
 tected as the trimethylsilyl derivatives. N.m.r.  
 spectra were measured in deuterated acetone.



| No. | R <sup>4</sup>           | X                                  | Y   |
|-----|--------------------------|------------------------------------|-----|
| 46  | phenyl                   | —CH <sub>2</sub> —                 | —O— |
| 47  | phenyl                   | —CH(CH <sub>3</sub> )—             | —O— |
| 48  | phenyl                   | —(CH <sub>2</sub> ) <sub>3</sub> — | —O— |
| 49  | 1-naphthyl               | —CH <sub>2</sub> —                 | —O— |
| 50  | 2-naphthyl               | —CH <sub>2</sub> —                 | —O— |
| 51  | 4-chlorophenyl           | —CH <sub>2</sub> —                 | —O— |
| 52  | 4-chlorophenyl           | —CH <sub>2</sub> —                 | —S— |
| 53  | 3-chlorophenyl           | —CH <sub>2</sub> —                 | —O— |
| 54  | 2-chlorophenyl           | —CH <sub>2</sub> —                 | —O— |
| 55  | 4-chlorophenyl           | —C(CH <sub>3</sub> ) <sub>2</sub>  | —O— |
| 56  | 4-bromophenyl            | —CH <sub>2</sub> —                 | —O— |
| 57  | 4-fluorophenyl           | —CH <sub>2</sub> —                 | —O— |
| 58  | 3-fluorophenyl           | —CH <sub>2</sub> —                 | —O— |
| 59  | 2-fluorophenyl           | —CH <sub>2</sub> —                 | —O— |
| 60  | 2,4-dichlorophenyl       | —CH <sub>2</sub> —                 | —O— |
| 61  | 2,5-dichlorophenyl       | —CH <sub>2</sub> —                 | —O— |
| 62  | 3,5-dichlorophenyl       | —CH <sub>2</sub> —                 | —O— |
| 63  | 4-tolyl                  | —CH <sub>2</sub> —                 | —O— |
| 64  | 3-tolyl                  | —CH <sub>2</sub> —                 | —O— |
| 65  | 2-tolyl                  | —CH <sub>2</sub> —                 | —O— |
| 66  | 3,5-xylyl                | —CH <sub>2</sub> —                 | —O— |
| 67  | 4-chloro-3-methyl-phenyl | —CH <sub>2</sub> —                 | —O— |
| 68  | 2-chloro-4-methyl-phenyl | —CH <sub>2</sub> —                 | —O— |
| 69  | 3-trifluoromethyl-phenyl | —CH <sub>2</sub> —                 | —O— |
| 70  | 4-methoxyphenyl          | —CH <sub>2</sub> —                 | —O— |
| 71  | 2-methoxyphenyl          | —CH <sub>2</sub> —                 | —O— |
| 72  | 4-chloro-1-naphthyl      | —CH <sub>2</sub> —                 | —O— |

| No. | Isomer* | Characterising Data   |
|-----|---------|---|
| 46  | mixed   | $R_F = 0.2$ (acetone/cyclohexane/ethyl acetate—1:1:2)<br>N.m.r.: $\delta$ 6.98—7.28 (5H, aromatic), 5.48 (2H, cis olefin), 5.78 (2H, trans olefin), 3.5—4.5 (5H, $>CH_2O$ and $-COOH$ ) |
| 47  | mixed   | $M^+ = 589.3267$ [calculated 589.3255 for methyl ester, 9-methoxime, 11,15-di(trimethylsilyl) derivative]. $R_F = 0.4$ (3% acetic acid in ethyl acetate)                                |
| 48  | mixed   | $R_F = 0.3$ (3% acetic acid in ethyl acetate)   |
| 49  | mixed   | $R_F = 0.4$ (3% acetic acid in ethyl acetate).<br>N.m.r.: aromatic protons at $\delta$ 8.3—8.5 (1H), 7.7—7.9 (1H), 7.2—7.5 (4H) and 6.8—7.08 (1H)                                       |
| 50  | mixed   | $R_F = 0.3$ (3% acetic acid in ethyl acetate).<br>N.m.r.: aromatic protons at $\delta$ 7.7—7.8 (3H) and 7.1—7.5 (4H)  |
| 51  | mp      | $M^+ = 609.2633$ [calculated 609.2709 for methyl ester, 9-methoxime, 11,15-di(trimethylsilyl) derivative]. $R_F = 0.4$ (3% acetic acid in ethyl acetate)                                |
| 52  | mixed   | $R_F = 0.5$ (3% acetic acid in ethyl acetate).<br>N.m.r.: aromatic protons at $\delta$ 7.3 (4H)   |
| 53  | mp      | $R_F = 0.3$ (3% acetic acid in ethyl acetate).<br>N.m.r.: aromatic protons at $\delta$ 7.15 (1H) and 6.9 (3H)   |
| 54  | mixed   | $R_F = 0.4$ (3% acetic acid in ethyl acetate).  |
| 55  | mixed   | $R_F = 0.5$ (3% acetic acid in ethyl acetate).<br>N.m.r.: aromatic protons at $\delta$ 7.28 (2H), 7.19 (2H) and 2 methyls at $\delta$ 1.25 and 1.30 (6H)                                |
| 56  | mixed   | $M^+ = 509.1417$ (calculated 509.1413 for methyl ester, 9-methoxime)  |
| 57  | mixed   | $R_F = 0.3$ (3% acetic acid in ethyl acetate)<br>N.m.r.: aromatic protons at $\delta$ 6.91 (2H) and 7.08 (2H)   |
| 58  | mixed   | $R_F = 0.3$ (2% acetic acid in ethyl acetate).<br>N.m.r.: aromatic protons at $\delta$ 7.25 (1H) and 6.65 (3H)  |

| No. | Isomer* | Characterising Data  |
|-----|---------|--|
| 59  | mixed   | $R_F = 0.4$ (5% acetic acid in ethyl acetate).<br>N.m.r.: aromatic protons at $\delta$ 7.05 (4H)   |
| 60  | mixed   | $R_F = 0.4$ (0.25% acetic acid in ethyl acetate)<br>N.m.r.: aromatic protons at $\delta$ 7.12 (1H), 7.3 (1H) and 7.41 (1H)                           |
| 61  | mixed   | $R_F = 0.34$ (3% acetic acid in ethyl acetate).<br>N.m.r.: aromatic protons at $\delta$ 7.3 (1H), 7.15 (1H) and 6.9 (1H)                             |
| 62  | mixed   | $R_F = 0.34$ (3% acetic acid in ethyl acetate).<br>N.m.r.: aromatic protons at $\delta$ 6.9 (3H)   |
| 63  | mixed   | $R_F = 0.2$ (cyclohexane/ethyl acetate/acetone, 2:2:1).<br>N.m.r.: aromatic protons at $\delta$ 6.7 (2H) and 7.1 (2H), and methyl at $\delta$ 2.28   |
| 64  | mixed   | $R_F = 0.5$ (3% acetic acid in ethyl acetate).<br>N.m.r.: aromatic protons at $\delta$ 7.05 (1H) and 6.73 (3H), and methyl at $\delta$ 2.28          |
| 65  | mixed   | $M^+ = 589.3284$ [calculated 589.3254 for methyl ester, methoxime, di(trimethylsilyl) derivative].<br>$R_F = 0.35$ (3% acetic acid in ethyl acetate) |
| 66  | mixed   | $R_F = 0.2$ (cyclohexane/acetone/ethyl acetate—4:1:2).<br>N.m.r.: aromatic protons at $\delta$ 6.5 (3H), and methyls (6H) at 2.28                    |
| 67  | mixed   | $R_F = 0.5$ (5% acetic acid in ethyl acetate).<br>N.m.r.: aromatic protons at $\delta$ 7.2 (1H) and 6.85 (2H), and methyl at 2.3                     |
| 68  | mixed   | $R_F = 0.4$ (cyclohexane/ethyl acetate/acetone—4:2:1).<br>N.m.r.: aromatic protons at $\delta$ 7.18 (1H) and 6.80 (2H), and methyl at 2.2            |
| 69  | mp      | $R_F = 0.5$ (5% acetic acid in ethyl acetate).<br>N.m.r.: aromatic protons at $\delta$ 7.5 (1H) and 7.25 (3H)  |
| 70  | mixed   | $R_F = 0.6$ (3% acetic acid in ethyl acetate)  |
| 71  | mixed   | $R_F = 0.65$ and 0.7 (3% acetic acid in ethyl acetate)   |
| 72  | mixed   | $R_F = 0.4$ (3% acetic acid in ethyl acetate).<br>N.m.r.: aromatic protons at $\delta$ 8.4 (1H), 8.15 (1H), 7.6 (3H) and 7.08 (1H)                   |

\* mp = more polar.

5 The 9-oxo prostanoic acid derivatives used as starting materials may be obtained by oxidation of the corresponding 9 $\alpha$ -hydroxy compound, as exemplified below for the preparation of 9 - oxo - 16 - phenoxy - 11 $\alpha$ ,15-bis(tetrahydropyran - 2 - yloxy) - 17,18,19,20-tetranor - 5 - cis - 13 - trans - prostadienoic acid:

10 To a solution of 9 $\alpha$  - hydroxy - 16 - phenoxy - 11 $\alpha$ ,15 - bis(tetrahydropyran - 2 - yloxy) - 17,18,19,20 - tetranor - 5 - cis - 13 - trans - prostadienoic acid (270 mg.) in acetone (5 ml.) at -10° C. was added Jones' reagent (chromic acid in acetone), 0.163 ml.). After 15 minutes, isopropanol (1 drop) was added, followed by ethyl acetate (20 ml). The solution was washed with 1:1 saturated brine/water, and was dried. Evaporation of the solvents, and chromatography of the residue on silica, using 1:1 ether/petroleum ether (b.p. 40-60° C.) as eluting solvent, gave the required 9-oxo-bis(tetrahydropyranyl ether), R<sub>F</sub> = 0.2 (50% ethyl acetate in toluene).

25 Example 11.  
The process described in Example 3 was repeated, using 11 $\alpha$ ,15 - dihydroxy - 16 - (2-naphthoxy) - 9 - oxo - 17,18,19,20 - tetranor - 5 - cis - 13 - trans - prostadienoic acid, in place of 16 - (4 - chlorophenoxy)-30 9 $\alpha$ ,11 $\alpha$ ,15 - trihydroxy - 17,18,19,20 - tetranor - 5 - cis - 13 - trans - prostadienoic acid, to give methyl 11 $\alpha$ ,15 - dihydroxy - 16 - (2-naphthoxy) - 9 - oxo - 17,18,19,20 - tetranor - 5 - cis - 13 - trans - prostadienoate, R<sub>F</sub> = 0.3 (ethyl acetate).

35 Example 12.  
To a solution of 16 - (4 - chlorophenylthio) - 9 $\alpha$ ,11 $\alpha$ ,15 - trihydroxy - 17,18,19,20-tetranor - 5 - cis - 13 - trans - prostadienoic acid (12 mg.) in methanol (0.5 ml.) at 0° C. 40 was added a solution of sodium periodate (5 mg.) in water (0.5 ml.). After 18 hours the solvents were evaporated, and the residue was extracted with acetone to give 16 - (4-chlorophenylsulphiny) - 9 $\alpha$ ,11 $\alpha$ ,15 - trihydroxy - 17,18,19,20 - tetranor - 5 - cis - 45 13 - trans - prostadienoic acid, M<sup>+</sup> = 744.2918 (calculated 744.2956), R<sub>F</sub> = 0.2 (3% acetic acid in ethyl acetate).

|    |  |        |
|----|--|--------|
| 50 | Example 13.  | % w/v  |
| 55 | 16 - (4 - fluorophenoxy) - 9 $\alpha$ ,11 $\alpha$ ,15-trihydroxy - 17,18,19,20 - tetranor - 5 - cis - 13 - trans - prostadienoic acid | 0.003  |
|    | Sodium phosphate   | 2.90   |
|    | Sodium hydrogen phosphate  | 0.30   |
|    | Water for injection  | to 100 |

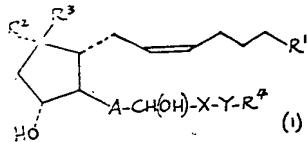
60 The sodium phosphate was dissolved in about 80% of the water, followed by the prostadienoic acid derivative, and, when

dissolved, the sodium hydrogen phosphate. The solution was made up to volume with water for injection, and the pH was checked to be between 6.7 and 7.7. The solution was filtered to remove particulate matter, sterilised by filtration, and filled into presterilised neutral glass ampoules under aseptic conditions. Immediately before use, the contents of an ampoule are diluted in sodium chloride B.P. for administration by intravenous infusion.

The prostadienoic acid derivative may, of course, be replaced by an equivalent amount of another prostanoic acid derivative of the invention.

#### WHAT WE CLAIM IS:—

1. A prostanoic acid derivative of the formula:—



wherein R<sup>1</sup> is a hydroxymethyl or carboxy radical, or an alkoxy carbonyl radical of up to 11 carbon atoms; either R<sup>2</sup> is a hydroxy radical or an alkanoyloxy radical of 1 to 4 carbon atoms and R<sup>3</sup> is a hydrogen atom, or R<sup>2</sup> and R<sup>3</sup> together form the oxo radical; A is an ethylene or trans-vinylene radical; X is an alkylene radical of 1 to 3 carbon atoms bearing as substituents 0, 1 or 2 alkyl radicals, each of 1 to 3 carbon atoms; Y is an oxygen or sulphur atom, a sulphinyl (-SO-) radical or an alkylimino (-NAlkyl-) radical of up to 4 carbon atoms; and R<sup>4</sup> is an aryl, benzyl or furfuryl radical which is unsubstituted or which is substituted by halogen atoms, hydroxy, nitro or phenyl radicals, alkyl, alkenyl, halogenoalkyl, alkoxy, alkenyloxy or acylamino radicals of up to 4 carbon atoms or dialkylamino radicals wherein each alkyl is of 1 to 3 carbon atoms; which compound contains 0 or 1 alkyl radical of up to 4 carbon atoms on carbon atom 2, 3 or 4; and for those compounds wherein R<sup>1</sup> is a carboxy radical, the pharmaceutically acceptable salts thereof.

2. A prostanoic acid derivative as claimed in claim 1 wherein R<sup>1</sup> is a hydroxymethyl, carboxy, methoxycarbonyl, ethoxycarbonyl, n-butoxycarbonyl or n-decyloxycarbonyl radical; R<sup>2</sup> is a hydroxy, acetoxy or propionyloxy radical and R<sup>3</sup> is a hydrogen atom, or R<sup>2</sup> and R<sup>3</sup> together form the oxo radical; A has the meaning defined in claim 1; X is a methylene, ethylene or trimethylene radical bearing 0, 1 or 2 methyl substituents; Y is an oxygen or sulphur atom, or the sulphinyl or methylimino radical; and R<sup>4</sup> is a phenyl, naphthyl, benzyl or furfuryl radical containing as substituents not more than two halogen

atoms, phenyl, hydroxy, methyl, t-butyl, allyl, methoxy or allyloxy radicals, chloroalkyl or fluoroalkyl radicals each of 1 to 4 carbon atoms or dimethylamino radicals; which compound contains 0 or 1 alkyl radicals of up to 4 carbon atoms on carbon atom 2, 3 or 4; and for those compounds wherein R<sup>1</sup> is a carboxy radical the ammonium, alkylammonium containing 1 to 4 alkyl radicals each of 1 to 6 carbon atoms, alkanolammonium containing 1 to 3 2-hydroxyethyl radicals, and alkali metal salts thereof.

3. A prostanoic acid derivative of the formula I shown in claim 1, wherein R<sup>1</sup> is a hydroxymethyl, carboxy, methoxycarbonyl, ethoxycarbonyl or n-butoxycarbonyl radical; R<sup>2</sup> is a hydroxy or acetoxy radical and R<sup>3</sup> is a hydrogen atom, or R<sup>2</sup> and R<sup>3</sup> together form the oxo radical; A is the ethylene or trans-vinylene radical; X is the methylene, ethyldene, isopropylidene or trimethylene radical; Y is an oxygen or sulphur atom, or the sulphinyl or methylimino radical; and R<sup>4</sup> is the furfuryl or benzyl radical, or a phenyl or naphthyl radical containing as substituents not more than two chlorine, bromine or fluorine atoms, or phenyl, hydroxy, methyl, t-butyl, allyl, methoxy, trifluoromethyl or dimethylamino radicals; which compound optionally bears a methyl substituent on carbon atom 2.

4. A prostanoic acid derivative as claimed in any preceding claim wherein R<sup>4</sup> is a chlorophenyl, chloronaphthyl, bromophenyl, fluorophenyl, tolyl, xylyl, methylnaphthyl, t-butylphenyl, methylchlorophenyl, trifluoromethylphenyl, hydroxyphenyl, methoxyphenyl, methoxynaphthyl, biphenyl, dimethylaminophenyl or tetrahydronaphthyl radical.

5. A prostanoic acid derivative as claimed in any preceding claim wherein R<sup>4</sup> is the phenyl, benzyl, furfuryl, 1-naphthyl, 2-naphthyl, 2-, 3- or 4-chlorophenyl, 4-bromophenyl, 2-, 3- or 4-fluorophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dichlorophenyl, 2-, 3- or 4-tolyl, 2,3-, 3,4- or 3,5-xylyl, 4-t-butylphenyl, 4-allylphenyl, 3-trifluoromethylphenyl, hydroxyphenyl, 2-, 3- or 4-methoxyphenyl, 4-biphenyl, 3-dimethylaminophenyl, 2-chloro-4-methylphenyl, 4-chloro-3-methylphenyl, 1-chloro-2-naphthyl, 4-chloro-2-naphthyl, 6-methyl-2-naphthyl, 6-methoxy-2-naphthyl or 5,6,7,8-tetrahydro-2-naphthyl radical.

6. A prostanoic acid derivative of the formula I shown in claim 1, wherein R<sup>1</sup> is a carboxy radical or an alkoxy carbonyl radical of up to 6 carbon atoms; either R<sup>2</sup> is a hydroxy radical or an alkanoyloxy radical of 1 to 4 carbon atoms and R<sup>3</sup> is a hydrogen atom, or R<sup>2</sup> and R<sup>3</sup> together form the oxo radical; A is an ethylene or trans-vinylene radical; X is an alkylene radical of 1 to 3 carbon atoms bearing as substituents 0, 1 or 2 alkyl radicals, each of 1 to 3 carbon atoms; and R<sup>4</sup> is an aryl radical, which is unsubstituted

or which is substituted by halogen atoms, nitro radicals, alkyl, alkoxy or acylamino radicals of 1 to 4 carbon atoms or dialkylamino radicals wherein each alkyl is of 1 to 3 carbon atoms; and for those compounds wherein R<sup>1</sup> is a carboxy radical, pharmaceutically acceptable salts thereof.

7. A prostanoic acid derivative of the formula I given in claim 1 wherein R<sup>1</sup> is a hydroxymethyl or carboxy radical, or an alkoxy carbonyl radical of up to 7 carbon atoms; either R<sup>2</sup> is a hydroxy radical or an alkanoyloxy radical of 1 to 4 carbon atoms and R<sup>3</sup> is a hydrogen atom, or R<sup>2</sup> and R<sup>3</sup> together form the oxo radical; A is an ethylene or trans-vinylene radical; X is an alkylene radical of 1 to 3 carbon atoms bearing as substituents 0, 1 or 2 alkyl radicals, each of 1 to 3 carbon atoms; and R<sup>4</sup> is an aryl or benzyl radical, which is unsubstituted or which is substituted by halogen atoms, nitro or phenyl radicals, alkyl, halogenoalkyl, alkoxy or acylamino radicals of 1 to 4 carbon atoms or dialkylamino radicals wherein each alkyl is of 1 to 3 carbon atoms; and those compounds wherein R<sup>1</sup> is a carboxy radical, pharmaceutically acceptable salts thereof.

8. A prostanoic acid derivative as claimed in any one of claims 1, 2, 3, 6 and 7 wherein R<sup>4</sup> is a chlorophenyl, fluorophenyl, trifluoromethyl or unsubstituted naphthyl radical.

9. A prostanoic acid derivative as claimed in any one of claims 1, 2, 3, 6 and 7 wherein R<sup>1</sup> is a carboxy or methoxycarbonyl radical and R<sup>4</sup> is a chlorophenyl, fluorophenyl, trifluoromethyl or unsubstituted naphthyl radical.

10. A prostanoic acid derivative as claimed in any one of claims 1, 2, 3 and 7 wherein R<sup>1</sup> is the hydroxymethyl radical and R<sup>4</sup> is a chlorophenyl, fluorophenyl, trifluoromethyl or unsubstituted naphthyl radical.

11. A prostanoic acid derivative as claimed in any one of claims 8, 9 and 10 wherein R<sup>4</sup> is the 3- or 4-chlorophenyl, 2- or 4-fluorophenyl, 3-trifluoromethylphenyl or 2-naphthyl radical.

12. A prostanoic acid derivative of the formula I given in claim 1, wherein R<sup>1</sup> is the carboxy or methoxycarbonyl radical, R<sup>2</sup> is the hydroxy radical and R<sup>3</sup> is a hydrogen atom or R<sup>2</sup> and R<sup>3</sup> together form the oxo radical, A is the trans-vinylene radical, X is the methylene or isopropylidene radical, Y is an oxygen atom and R<sup>4</sup> is the 3- or 4-chlorophenyl, 2- or 4-fluorophenyl, or 2-naphthyl radical.

13. A prostanoic acid derivative of the formula I given in claim 1 wherein R<sup>1</sup> is the carboxy, methoxycarbonyl or hydroxymethyl radical, R<sup>2</sup> is a hydroxy radical and R<sup>3</sup> is a hydrogen atom, or R<sup>2</sup> and R<sup>3</sup> together form the oxo radical, A is the trans-vinylene radical, X is the methylene or isopropylidene radical, Y is an oxygen atom and R<sup>4</sup> is the 3-

or 4-chlorophenyl, 2- or 4-fluorophenyl, 3-trifluoromethylphenyl or 2-naphthyl radical.

14. A prostanoid acid derivative as claimed in claim 12 or 13 which additionally bears a methyl substituent on carbon atom 2.

15. The compounds 16 - (4 - fluorophenoxy) - 9 $\alpha$ ,11 $\alpha$ ,15 - trihydroxy - 17,18,19,20-tetranor - 5 - cis - 13 - trans - prostadienoic acid, methyl 16 - (4 - fluorophenoxy) - 9 $\alpha$ ,11 $\alpha$ ,15 - trihydroxy - 17,18,19,20 - tetranor - 5 - cis - 13 - trans - prostadienoate, 16 - (2 - fluorophenoxy) - 9 $\alpha$ ,11 $\alpha$ ,15 - trihydroxy - 17,18,19,20 - tetranor - 5 - cis - 13 - trans - prostadienoic acid, 16 - (4-chlorophenoxy) - 9 $\alpha$ ,11 $\alpha$ ,15 - trihydroxy - 17,18,19,20 - tetranor - 5 - cis - 13 - trans - prostadienoic acid, methyl 16 - (4 - chlorophenoxy) - 9 $\alpha$ ,11 $\alpha$ ,15 - trihydroxy - 17,18,19,20 - tetranor - 5 - cis - 13 - trans - prostadienoate, 16 - (3 - chlorophenoxy) - 9 $\alpha$ ,11 $\alpha$ ,15 - trihydroxy - 17,18,19,20 - tetranor - 5 - cis - 13 - trans - prostadienoic acid, methyl 16 - (3 - chlorophenoxy) - 9 $\alpha$ ,11 $\alpha$ ,15 - trihydroxy - 17,18,19,20 - tetranor - 5 - cis - 13 - trans - prostadienoate, 9 $\alpha$ ,11 $\alpha$ ,15-trihydroxy - 16 - (2 - naphthoxy) - 17,18,19,20 - tetranor - 5 - cis - 13 - trans - prostadienoic acid, and 16 - (4 - chlorophenoxy) - 9 $\alpha$ ,11 $\alpha$ ,15 - trihydroxy - 16,16-dimethyl - 17,18,19,20 - tetranor - 5 - cis - 13 - trans - prostadienoic acid.

16. The compounds 16 - (4 - chlorophenoxy) - 9 $\alpha$ ,11 $\alpha$ ,15 - trihydroxy - 17,18,19,20-tetranor - 5 - cis - 13 - trans - prostadienol and 9 $\alpha$ ,11 $\alpha$ ,15 - trihydroxy - 16 - (3 - trifluoromethylphenoxy) - 17,18,19,20 - tetranor - 5 - cis - 13 - trans - prostadienoic acid.

17. The compound 16 - (3 - chlorophenoxy) - 9 $\alpha$ ,11 $\alpha$ ,15 - trihydroxy - 2-methyl - 17,18,19,20 - tetranor - 5 - cis - 13 - trans - prostadienol.

18. The compound 16 - (4 - chlorophenoxy) - 11 $\alpha$ ,15 - dihydroxy - 9 - oxo - 17,18,19,20 - tetranor - 5 - cis - 13 - trans - prostadienoic acid.

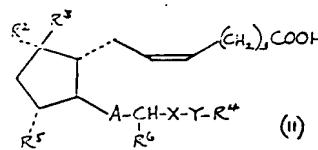
19. A compound as claimed in any preceding claim which is the more polar of the C-15 epimers as shown by thin layer chromatography.

20. A compound as claimed in any preceding claim which is in a racemic form.

21. A compound as claimed in any one of claims 1 to 19 which is in a luteolytically effective, optically-active form.

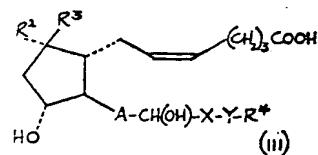
22. A process for the manufacture of a prostanoid acid derivative as claimed in claim 1 which comprises:

- (a) for those compounds wherein R<sup>1</sup> is a carboxy radical, the hydrolysis of a compound of the formula:



or of a mixed anhydride thereof, wherein A, X, Y, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> have the meanings stated above, and R<sup>5</sup> and R<sup>6</sup> are each a tetrahydro-pyran-2-yloxy radical, or an acyloxy radical of 1 to 6 carbon atoms, whereafter when a salt is required the product is reacted with a base; or

(b) for those compounds wherein R<sup>1</sup> is an alkoxy carbonyl radical of up to 11 carbon atoms, the reaction of an acid of the formula:

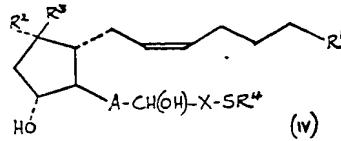


wherein A, X, Y, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> have the meanings stated above, with a diazoalkane of the formula R'.N<sub>2</sub>, wherein R' is an alkyl radical of 1 to 10 carbon atoms; or

(c) for those compounds wherein R<sup>1</sup> is an alkoxy carbonyl radical of up to 11 carbon atoms, the reaction of a salt of an acid of the formula II with an alkyl halide of 1 to 10 carbon atoms; or

(d) for those compounds wherein R<sup>1</sup> is the hydroxymethyl radical and Y is an oxygen or sulphur atom or an alkylimino radical, the reduction of an ester of the formula I wherein R<sup>1</sup> is an alkoxy carbonyl radical of up to 11 carbon atoms; or

(e) for those compounds wherein Y is the sulphinyl radical, the oxidation of a thio-compound of the formula:



wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, A and X have the meanings defined in claim 1.

23. A process as claimed in claim 22 wherein the hydrolysis is carried out in an aqueous or alcoholic solution of an alkali metal carbonate.

24. A process as claimed in claim 22 which

is carried out with a solution of potassium carbonate in methanol.

25. A process as claimed in claim 22 wherein the salt of an acid of the formula II  
5 is the silver salt.

26. A process as claimed in claim 22 wherein the alkyl halide is an alkyl iodide.

27. A process as claimed in claim 22 wherein the reduction is carried out with a complex  
10 metal hydride.

28. A process as claimed in claim 27 wherein the complex metal hydride is lithium aluminium hydride.

29. A process as claimed in claim 22 wherein  
15 the oxidation is carried out with sodium perio-  
date.

30. A pharmaceutical or veterinary com-  
position which comprises a prostanoic acid  
20 derivative as claimed in claim 1 together with  
a pharmaceutically or veterinarianily acceptable  
diluent or carrier.

31. A composition as claimed in claim 30  
which is in a form suitable for oral ad-  
ministration, for inhalation, for parenteral ad-  
ministration, or for anal or vaginal use.  
25

32. A composition as claimed in claim 31  
which is a tablet, capsule, aerosol, solution suit-  
able for spraying, sterile injectable aqueous or  
oily solution or suspension, or a suppository.

33. A composition as claimed in claim 30  
which is a sterile, substantially aqueous  
solution containing from 0.01 to 10 µg./ml.  
30 of the prostanoic acid derivative.

34. A prostanoic acid derivative as claimed  
in claim 1 substantially as hereinbefore  
described in any one of Examples 1 to 12.

35. A prostanoic acid derivative as claimed  
in claim 6 substantially as hereinbefore  
described in Example 1.

36. A prostanoic acid derivative as claimed  
in claim 7 substantially as hereinbefore  
described in any one of Examples 1 to 3.

37. A pharmaceutical or veterinary com-  
position as claimed in claim 30 substantially as  
hereinbefore described in Example 13.

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